UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,703	07/31/2001	Gerald Krystal	50216/003004	6548

21559 7590 01/30/2003

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	9

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,703	KRYSTAL ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Applicant's election of Group I, claims 1-20 for examination (Paper No. 8) filed 2 December 2002 is acknowledged. Also, applicant's election with traverse of a single polypeptide SEQ ID NO:1 and a cardiovascular disease for examination in Paper No. 8 is acknowledged. The traversal is on the ground(s) that all the peptide sequences and the disease states recited in the claims should be examined together without an undue burden to examiner. The traversal has been fully considered but it is not persuasive.

The response comments that the polypeptides presented in the claims are closely related by sequence. The peptide sequences of SEQ ID NOs: 1-8 differ from one other; the amino acid sequence SEQ IO NO:1 (elected): SVDVEY is structurally distinct from the sequence SEQ ID NO:2: YVDVDT, for example. Therefore, the additional election requirement is applicable, and the structurally different sequences require separate search, which would result in an undue burden to examiner.

Further, the response comments that and that cell death is the common pathological characteristic shared by the diseases recited in the elected claim 18. This is found unpersuasive because cell death is not an intrinsic feature of the disease states rather a consequence of a disease. The pathological state or/and pathological mechanism of cardiovascular disease (elected) differs from that of a viral disease (non-elected); for instance, accelerated atherosclerosis is a common cause for myocardial infarction that is a type of cardiovascular disease, while a viral disease is commonly caused by viral infection. It is also of note that the response asserts that claims 14 and 18 do not recite any single disease. The argument is not persuasive since claim 18 recites the six different disease states. It would require therefore a

serious and undue burden on the examiner to have searched all disease states and additional subtype disease associated with the said disease (*e.g.*, acute coronary syndrome is a subtype of cardiovascular disease.

The claims will be examined insofar as to the elected patentably distinct peptide of Group I, SEQ ID NO:1 and the elected cardiovascular disease. Claims 21-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Since applicant elects cardiovascular disease for examination and claim 20 set forth none of disease states related to the elected disease, claim 20 is drawn to non-elected invention. Therefore, elected claims 1-19 together with the elected polypeptide and the disease sate are examined in this Office action.

Specification/Claim/ Objections

The disclosure is objected to because of the following informalities:

(1) In page 2, line 13, "HIV" should be spelled out in full at the first instance of use. See also page 4, line 4, "FALS"; page 12, line 7, "PNA"; page 13, line 20, "CMV" and "HSV", and line 27, "DEAE"; page 16, line 28, "AIDS"; page 19, line 18, "CK" and CK-MB"; page 19, line 24, "AZT".

(2) In page, 8, lines 1-2, "SEQ. ID. No. 13" and "SEQ. ID. No. 14" should be changed to "SEQ ID NO:13" and "SEQ ID NO: 14", respectively; the same type of changes should be made throughout the specification.

(3) In page 8, line 29 "see eg., SEQ I.D. No. 13, 14..." should be changed to "see *e.g.*, SEQ ID NO: 13, 14...".

(4) In page 1, line 2, "now pending" should be updated to "US Pat. No. 6348567" because Application No. 09294457 is now a patent.

(5) Claims 2-3 and 16-18 are objected to as reciting non-elected subject matter (sequences SEQ ID NO:2 through SEQ ID NO:8) and non-elected diseases, *i.e.*, a neurodegenerative disorder, an immune disease, a neoplastic disorder, an inflammatory disorder and a viral disease.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 12, 14 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synthesis and purification of streptokinase-derived peptide fragments, and amelioration of cell death by synthesized peptides thereof in cultured cells and isolated organ, does not reasonably provide enablement for a method of preventing cell death in warm-blood animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does

not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/The nature of the invention:

Claims 1 and 14 of the current application sets forth a method of treating or preventing cell death in a warm-blood animal comprising disserting to the animal the claimed peptides having the core sequence VDV (Val-Asp-Val).

The issue herein is whether or not the claimed method would function "for preventing or treating cell death in a mammal (warm-blood animal), which is associated with cardiovascular disease (see claims and 18-19). The nature of the invention is such that it would require the administration of the synthesized peptide containing the core sequence that would prevent a mammalian subject from cell death in cardiovascular system and from having cardiovascular disease thereof. The exemplification is drawn to ameliorate cell death in the investigated subjects, as indicated by decrease of percent of cell death in comparison to a control, *i.e.*, untreated with the claimed peptides or in a dose-response pharmacology wherein decrease of the number of cell death is proportional to increase of the peptide concentration applied to the subject cells. The specification sets forth working examples with respect to amelioration of cell death by synthesized streptokinase peptide fragments thereof in cultured cardiac myocytes

(examples 1 and 3), in human hematopoietic cell line (examples 5 and 6), and in isolated intact rat heart (example 4). Yet, the specification does not provide working example and insufficient guidance and teaching regarding preventing or treating cell death in cardiovascular tissues or/and organs. Thus, the claim language "treating or preventing cell death" would render the claims so broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

Cell death in an animal is a biological and genetic process that is irreversible and unpreventable or unavoidable, thus, untreatable. The current application provides no guidance and working examples as to how cell death can be completely avoided, *i.e.*, prevented, or treated (100% cured). Applicant is therefore not in possession of method of preventing or treating cell growth in a warm-blooded animal comprising administering to said animal the peptide(s) claimed, but applicant is in possession of the method of reducing or ameliorating cell death in cardiovascular tissue or organ associated with a cardiovascular disease state. The application needs to provide sufficient written description regarding this in order for enablement.

Claim 14 sets forth "a derivative or analog" of the streptokinase peptide that ameliorates cell death. Yet, the specification is silent in synthesis, purification and use of the peptide analog in preventing or treating cell death. The specification provides no working examples or representative examples as to preventing or treating cell death with the analog peptide. The specification teaching does not establish actual reduction to practice since the claimed peptide analog or derivative has not been actually isolated or purified, characterized and tested for, at least, amelioration of the cardiac myocyte cell death. Thus, applicant is not in possession of use of the peptide analog or derivative for treating or preventing the cell death. In this regard, the

application also needs to provide sufficient written description regarding this in order for enablement.

(2) The amount of direction or guidance presented:

The specification does not disclose one reasonable method for preventing cell death in a mammal or a method of treating, (*i.e.*, 100% curing disease) cell death in the subject suffering cardiovascular disease which bears a reasonable correlation to the entire scope of the claims. The specification lacks guidance/direction as to how the claimed peptides prevent cell death to render the subject animal survival without death, and as to the peptide analog (genus) that encompasses chemical (modification), genetic (naturally-occurring mutation) and recombinant (protein engineering product). The specification needs to provide what is missing in this regard so as to enable same.

(3) The unpredictability of the art:

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since culture cardiac myocyte cells and an isolated mammal heart were used for addressing amelioration of cell death *in vivo*, such studies have not correlated well with *in vivo* clinical trial results in patients as to preventing cell death. The specification does not teach how to extrapolate data obtained from amelioration of cell death in the cultured cardiac myocytes or an isolated heart of a mammal *in vitro* including human therapeutic prevention, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the consequence of treating a cardiovascular disease by preventing cell death is highly variable.

In addition, the analog peptides deviated from the core structure (VDV) or modification or mutation in the core motif are unpredictable and would not mediate amelioration of cell death. Honig *et al.* teach that the amino acid residues of a protein that can tolerate structural change (*e.g.*, mutations: conservative substitution or no substitution, addition or deletion), which are critical to maintain the protein's structure, will require guidance (see *Honig, B.* (1999) *J. Mol. Biol.* 293, 283-293). Given the lack of sufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NO:1 that after truncation or deletion, substitution and other structural modification will retain the same structure as SEQ ID NO:1 is unpredictable. Thus, structural variant of the streptokinase peptides is an unpredictable variable in view of biological function, *e.g.*, ameliorating or preventing cell death.

Thus, the invention is unpredictable in the absence of factual indicia to the contrary.

(4) The quantity of experimentation necessary:

In the absence of working examples with regard to the numerous streptokinase peptide fragments or analogs for treating a cardiac disease state, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and error to practice the claimed invention as to preventing cell death. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the streptokinase peptide analogs, and for testing for ability of the peptide or analogs thereof to prevent cell death in the studied subject.

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of the peptides or analogs thereof. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a cell biologist or a physician with several years of experience in molecular biology as well as knowledge in cardiology and pharmacology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable essentially as directed to preventing cell death. An unduly level of skill is needed for the skilled artisan in order to establish a process suitable for preventing or treating cell death in a mammal, and for treating a cardiovascular disease state by a mean, *e.g.*, preventing cell death in cardiovascular tissues or organs.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue to practice the claimed method in regard to preventing cell death.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 2-3, and 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The dependent claims are also included in the rejection.

Claim 3 is indefinite as to how it is further limiting of claim 2 in regard to the recited sequences as to "comprises" in claim 2 and "has" in claim 3, each is open-ended and therefore the limitation is the recited sequence identification numbers.

Also, claims 16 and 17 recite "has" and "comprises", respectively. See the previous statement for the rejection to claim 3. Deletion or modification to eliminate redundancy is suggested.

Claim 12 is indefinite because of the double "a" before "neurodegenerative disorder". The dependent claims are also rejected.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14 and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobi, E. (US Pat. No. 4011142).

Jacobi teaches streptokinase treatment of myocardial infarcts (see column 1, lines 21-25). Because myocardial infarction refers to death of some of the muscle cells of the heart as a result of a lack of supply of oxygen and other nutrients, the Jacobi patent anticipates the claims 14, 18 and 19 of the current application.

Claims 1-3 and 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Madrazo, I. del C. T. *et al.*(US Pat. No. 6309873).

Madrazo *et al.* disclos the amino acid sequence of streptokinase comprising the core motif "Val-Asp-Val" (see SEQ ID NO:1), and teach streptokinase is used as a therapeutic agent in the treatment of disorders which causes of death of patient, *e.g.*, myocardial infarct (see column 1, lines 23-28). Therefore, the patent anticipates claims 1-3 and 12-19 of the current application. Note that claims 1-3 and 14-17 recite the open-ended language "comprising" as opposed to "consisting of" which is closed.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 12-19 are rejected under 35 U.S.C. 103(a) as being obvious over Gallus, A. S. (*Clin. Haemal.* (1986) 15, 509-559) taken with Jackson, K. W. *et al.* (Biochemistry (1982) 21, 6620-6625).

Gallus teaches that mortality after myocardial infraction is reduced (see table 4 at page 517) by administering to the patient streptokinase, and teaches SK therapy reduces the number of deaths among in-hospital patients (see Table 5, page 518, and the bridging pages 518-519). The Gallus' teaching is applied to claims 1, 12, 14 and 18-19 of the instant application. Claim 1 is included in the rejection because of the open-ended language "comprising" in the recitation "peptide comprising the amino acid sequence ..." as opposed to "consisting of" which is closed. Gallus reference thus would be applicable as a prior art against a claim reciting "comprising". For the same reason, claims 2 wherein recites "comprises", claim 3 wherein recites "has", claims 15 and 16 wherein recite "comprises", and claim 17 wherein recites "has", are also included in the rejection. Since Gallus also teaches reduction of patient death who is suffering myocardial infraction by streptokinase polypeptide (see page 516), and since non-medical term "heart attack" is "myocardial infarction" that means there is death of some of the muscle cells of the heart as a result of a lack of supply of oxygen and other nutrients, claim 13 is anticipated by the Gallus reference as well.

Jackson *et al.* disclose the amino acid sequence of streptokinase (see Figure 3) comprising Val-Asp-Val core motif, as applied to claims 1-3 and 12-19 of the instant application.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references because the Gallus' reference teaches a reduction of patient death by streptokinase therapy (see page 518, the third paragraph) wherein streptokinase is administered to the patient suffering cardiovascular disease, *e.g.*, myocardial infarction, and because the streptokinase peptide sequence has been disclosed by Jackson *et al.* Based on the disclosed streptokinase structure, the skilled artisan would have been motivated to investigate and use the streptokinase the fragments thereof for their ability of ameliorating cell death associated with cardiovascular disease as taught by Gallus (see pages 516-518). Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 1-3 and 12-19 are rejected under 35 U.S.C. 103(a) as being obvious over Podlasek, S. J.G. T. (US Pat. No. 5342755) taken with Jackson, K. W. *et al.* (*Biochemistry* (1982) 21, 6620-6625).

Podlasek *et al.* teaches streptokinase treatment of myocardial infarction (see column 1, lines 53-68). Because myocardial infarction refers to death of some of the muscle cells of the heart as a result of a lack of supply of oxygen and other nutrients, and because the amino acid sequence of streptokinase comprising the core motif "Val-Asp-Val" is evidenced by Jackson, K. W. *et al.* (*Biochemistry* (1982) 21, 6620-6625, see column 12, line 64), the Podlasek patent makes obvious over claims 1-3 and 12-19 of the current application because when combined the cited references demonstrate using streptokinase to treat infarcts and that one would have been motivated to combine the references as one is inextricably led to the Jackson *at el.* reference

(cited in the US Pat No. 5342775) and shows the sequence of streptokinase which contains a "Val-Asp-Val" subsequence. Note that claims 1-3 and 14-17 recite the open-ended language "comprising" as opposed to "consisting of" which is closed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

January 20, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600